IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Lehman *et al.*

Serial No.: 09/821,139

Filed: March 29, 2001

For: NASAL ADMINISTRATION OF AGENTS FOR THE TREATMENT OF GASTROPARESIS

Confirmation No.: 5628

Group Art Unit: 1616

Examiner: Haghighatian, M.

Attorney Docket No.: 7960-131

DECLARATION UNDER 37 C.F.R. § 1.131 OF LAURA S. LEHMAN, DAVID TIERNEY, ANASTASSIOS D. RETZIOS, MICHAEL PETRONE, DAVID YOUNG, CAROL B. TRAPNELL AND RUTH OLIVER

Sir:

We, Laura S. Lehman, David Tierney, Anastassios D. Retzios, Michael Petrone, David Young, Carol B. Trapnell and Ruth Oliver declare that:

1. We, together are co-inventors of the invention claimed in the above-identified patent application.

2. We have reviewed the specification and pending claims of the above-identified patent application.

3. Questcor Pharmaceuticals, Inc. ("Questcor"), GloboMax LLC ("Globomax") and Shire, U.S., Inc. are Assignees of the above-identified application. Questcor is a corporate entity formed by the merger of RiboGene Inc. ("RiboGene") and Cypros Pharmaceutical Corp. in November 1999. Roberts Pharmaceuticals Corporation ("Roberts") merged with Shire Pharmaceuticals Group PLC ("Shire") in December 1999.

4. The compound metoclopramide, whose application to gastroparesis is claimed in the above-identified application, was being developed under the tradename, Emitasol® by the cooperative efforts of Roberts (now Shire), RiboGene (now Questcor) and GloboMax.

5. The above-identified patent application claims priority to U.S. provisional application, Serial No. 60/193,181 ("the '181 application"), filed on March 30, 2000.

6. The claims pending in the above-identified patent application recite methods for treating or reducing a symptom of gastroparesis via intranasal administration of metoclopramide. In particular independent Claim 21 recites a method that comprises intranasal administration of a therapeutically effective amount at a daily dosage for about 2 weeks to about 8 weeks, and independent Claim 30 recites a method that comprises administering a therapeutically effective amount at a daily dosage of between about 40 mg/day and about 160 mg/day.

7. To the best of our knowledge and belief, the package insert for Pramidin 10 and Pramidin 20 that is of record in the above-identified patent application, as IDS reference AE, was made available to the public when the product Pramidin was first sold by Crinos Industria Pharmacobiologica S.p.a., in Italy, in April 1999.

8. As explained in detail hereinbelow, Exhibits A-R, attached hereto, demonstrate that the subject matter claimed in the above-identified patent application was conceived of prior to April 1999, and diligence was exercised from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

9. In accordance with standard practice, the dates listed in the documents provided in Exhibits A-R have been redacted.

10. Exhibit A demonstrates that the subject matter of the pending claims was conceived prior to April 1999. Exhibit A is a copy of an excerpt of an Investigational New Drug Application, Form FDA 1571 and Study Synopsis included therein, accompanied by a cover letter from Dr. Haenick, Senior Manager of Regulatory Affairs at Roberts to Dr. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, FDA. Dr. Haenick was an employee of Roberts, acting under the direction of Roberts. We, the co-inventors devised the protocol in Study Synopsis.

11. Exhibits B-R demonstrate that diligence was practiced from prior to April 1999 to subsequent actual reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the parent '181 application. In addition to the dates, confidential, proprietary information has also been redacted for the documents at Exhibits B-R.

12. As discussed hereinbelow, Exhibits B-R, discussed in detail, below, demonstrate diligence in planning a clinical trial protocol that would ultimately demonstrate efficacy and safety of intranasal metoclopramide for the proposed indications at the dosage range for the duration of treatment set forth in the Study Synopsis.

13. Exhibit B is a copy of a letter from Dr. Haenick, Senior Manager of Regulatory Affairs at Roberts to Dr. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, FDA. The letter submits minutes from the End of Phase II meeting with the FDA. An item discussed at the meeting was FDA acceptance of the proposed randomized, double-blind, double-dummy, positive controlled clinical study, as set forth in the Study Synopsis, to compare metoclopramide 10 mg orally before meals and at bedtime and metoclopramide nasal spray at a dose that gives comparable systemic metoclopramide in patients with diabetic gastroparesis.

14. Exhibit C is a copy of meeting minutes from a Roberts/RiboGene Experts Meeting. Items discussed at the meeting include preservation of the blind, the duration of the trial, possible modifications to the symptom assessment tool, and inclusion and exclusion criteria.

15. Exhibit D is a copy of a letter from Dr. Haenick to Dr. Talarico at the FDA. The letter submits revisions to the Phase III protocol. The revised protocol adds a second metoclopramide intranasal dosing group (10 mg four times daily) and a placebo nasal spray group to the study. The proposed study design would consist of two 4-week treatment phases.

16. Exhibit E is a copy of a letter from Dr. Retzios to Dr. Tierney. The letter discusses a desire to get Emitasol® approved in as short a time as possible with proposed dates for a Steering Committee Meeting.

17. Exhibit F is a copy of a letter from Dr. Retzios to Dr. Petrone. The letter refers to published studies of the use of domperidone in the treatment of diabetic gastroparesis, one of which compares the results with non-nasally administered metoclopramide. The letter postulates the possible use of the studies' clinical trial protocol for the testing of intranasal metoclopramide. Clinical trial protocol issues such as randomization, statistical assumptions and questionnaire wording are discussed.

18. Exhibit G is a copy of a letter from Dr. Haenick to Dr. Retzios forwarding budget proposals from two contract research organizations to conduct a Phase III trial.

19. Exhibit H is a copy of a fax from Dr. Haenick to Dr. Retzios forwarding draft meeting minutes from a meeting of the Roberts' Task Force meeting. Meeting discussion topics included Chemistry, Manufacturing and Controls (CMC), nonclinical, and clinical programs. Timelines for development were also established.

20. Exhibit I is a copy of a letter from Dr. Talarico at FDA to Dr. Haenick with protocol recommendations for the proposed clinical trial. The FDA made protocol recommendations including a placebo arm in phase one of the study. Other recommendations included, *inter alia*, the addition of a global assessment of therapy and elimination of the proposed scratch off laminate label.

21. Exhibit J is a copy of minutes of a meeting that took place at Roberts Laboratories, Inc. Representatives from Roberts, RiboGene and GloboMax were present. Items discussed at the meeting included: formulation development, toxicology studies in rabbits and monkeys (a summary provided herein at Exhibits O and P), and review of FDA comments in response to the proposed Phase III clinical trial. The study design was adapted to address FDA recommendations, including the addition of a placebo arm and dropping the withdrawal phase of the study. The proposed, adapted clinical trial was a placebo-controlled, parallel design comparing both the 10 mg and 20 mg metoclopramide nasal spray patients to the placebo group. The duration of therapy was proposed to be 6 weeks. Exhibits O and P, discussed below at paragraphs 26 and 27, demonstrate that the milestones set during this meeting were successfully and timely achieved.

22. Exhibit K is a copy of the GloboMax Response to Dr. Retzios's Comments for Phase III Protocol. The summary provides GloboMax's responses to Dr. Retzio's comments and provides recommendations for the Phase III clinical trial. The recommendations addressed both the secondary and primary objectives of the proposed clinical trial.

23. Exhibit L is a copy of an e-mail from Dr. Retzios to Dr. Petrone (cc: to Dr. Haenick) in which Dr. Retzios discusses updating the definition of "serious" and "unexpected" drug experiences for the proposed Phase III clinical trial.

24. Exhibit M is a copy of an e-mail from Dr. Haenick to Dr. Retzios (cc: to Dr. Petrone and other employees at Roberts) disclosing decisions made regarding the Phase III protocol in light of GloboMax and Dr. Retzios's comments.

25. Exhibit N is a copy of an e-mail from Dr. Retzios to Dr. Petrone (cc: to F. Sasinowski and C. Casamento) disclosing Dr. Retzios's comments on GloboMax's analysis.

26. Exhibit O is a copy of a summary of a Final Report from Covance Laboratories Inc., ("Covance") for a study entitled "3-Month Intranasal Study with Metoclopramide Nasal Spray in Rabbits with a 1-Month Recovery". Covance is a development services company that performs animal testing. The timeline of the study was in accordance with the timeline established at the Robert's Task Force meeting (as discussed in the meeting minutes provided at Exhibit H).

27. Exhibit P is a copy of a summary of a Final Report from Covance, for a study entitled "3-Month Intranasal Study with Metoclopramide Nasal Spray in Cynomolgus Monkeys with a 1-Month Recovery". The timeline of the study was in accordance with the timeline established at the Robert's Task Force meeting (as discussed in the meeting minutes provided at Exhibit H).

28. Exhibit Q is a copy of the agenda for Meeting of the Emitasol® Project Review Meeting. Items on the agenda included, for example, pharmaceutical development, non-clinical toxicology studies, quality control and IND and NDA submissions.

29. Exhibit R is a copy of a summary of the Final Report from Huntingdon Life Sciences. Huntingdon conducted a toxicity study on behalf of Roberts. The study, entitled "Metoclopramide Toxicity Study by Intranasal Administration to Cynomolgus Monkeys for 13 Weeks" was necessary for the FDA.

30. We have reviewed Exhibits A-R. We hereby confirm that the work evidenced by the documents of Exhibits A-R and all the acts relied upon in this Declaration to establish a conception of the invention claimed in the above-identified patent application prior to April 1999, and continuing diligence from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

31. We, the co-inventors of the invention claimed in the above-identified patent application further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Respectfully submitted,

Date: May 10, 2003

Laura S. Lehman

Respectfully submitted,

Date: _____

David Tierney

Respectfully submitted,

Date: _____

Anastassios D. Retzios

Respectfully submitted,

Date: _____

Michael Petrone

Respectfully submitted,

Date: _____

_____
David Young

Respectfully submitted,

Date: _____

_____
Carol B. Trapnell

Respectfully submitted,

Date: _____

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Ruth Oliver

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2. We have reviewed the specification and pending claims of the above-identified patent application.

3. Questcor Pharmaceuticals, Inc. ("Questcor"), GloboMax LLC ("Globomax") and Shire, U.S., Inc. are Assignees of the above-identified application. Questcor is a corporate entity formed by the merger of RiboGene Inc. ("RiboGene") and Cypros Pharmaceutical Corp. in November 1999. Roberts Pharmaceuticals Corporation ("Roberts") merged with Shire Pharmaceuticals Group PLC ("Shire") in December 1999.

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8. As explained in detail hereinbelow, Exhibits A-R, attached hereto, demonstrate that the subject matter claimed in the above-identified patent application was conceived of prior to April 1999, and diligence was exercised from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

9. In accordance with standard practice, the dates listed in the documents provided in Exhibits A-R have been redacted.

10. Exhibit A demonstrates that the subject matter of the pending claims was conceived prior to April 1999. Exhibit A is a copy of an excerpt of an Investigational New Drug Application, Form FDA 1571 and Study Synopsis included therein, accompanied by a cover letter from Dr. Haenick, Senior Manager of Regulatory Affairs at Roberts to Dr. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, FDA. Dr. Haenick was an employee of Roberts, acting under the direction of Roberts. We, the co-inventors devised the protocol in Study Synopsis.

11. Exhibits B-R demonstrate that diligence was practiced from prior to April 1999 to subsequent actual reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the parent '181 application. In addition to the dates, confidential, proprietary information has also been redacted for the documents at Exhibits B-R.

12. As discussed hereinbelow, Exhibits B-R, discussed in detail, below, demonstrate diligence in planning a clinical trial protocol that would ultimately demonstrate efficacy and safety of intranasal metoclopramide for the proposed indications at the dosage range for the duration of treatment set forth in the Study Synopsis.

13. Exhibit B is a copy of a letter from Dr. Haenick, Senior Manager of Regulatory Affairs at Roberts to Dr. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, FDA. The letter submits minutes from the End of Phase II meeting with the FDA. An item discussed at the meeting was FDA acceptance of the proposed randomized, double-blind, double-dummy, positive controlled clinical study, as set forth in the Study Synopsis, to compare metoclopramide 10 mg orally before meals and at bedtime and metoclopramide nasal spray at a dose that gives comparable systemic metoclopramide in patients with diabetic gastroparesis.

14. Exhibit C is a copy of meeting minutes from a Roberts/RiboGene Experts Meeting. Items discussed at the meeting include preservation of the blind, the duration of the trial, possible modifications to the symptom assessment tool, and inclusion and exclusion criteria.

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22. Exhibit K is a copy of the GloboMax Response to Dr. Retzios's Comments for Phase III Protocol. The summary provides GloboMax's responses to Dr. Retzio's comments and provides recommendations for the Phase III clinical trial. The recommendations addressed both the secondary and primary objectives of the proposed clinical trial.

23. Exhibit L is a copy of an e-mail from Dr. Retzios to Dr. Petrone (cc: to Dr. Haenick) in which Dr. Retzios discusses updating the definition of "serious" and "unexpected" drug experiences for the proposed Phase III clinical trial.

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28. Exhibit Q is a copy of the agenda for Meeting of the Emitasol® Project Review Meeting. Items on the agenda included, for example, pharmaceutical development, non-clinical toxicology studies, quality control and IND and NDA submissions.

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30. We have reviewed Exhibits A-R. We hereby confirm that the work evidenced by the documents of Exhibits A-R and all the acts relied upon in this Declaration to establish a conception of the invention claimed in the above-identified patent application prior to April 1999, and continuing diligence from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

31. We, the co-inventors of the invention claimed in the above-identified patent application further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Respectfully submitted,

Date: _____

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Laura S. Lehman

Respectfully submitted,

Date: _____

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Michael Petrone

Respectfully submitted,

Date: _____

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David Young

Respectfully submitted,

Date: _____

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Carol B. Trapnell

Respectfully submitted,

Date: 12 May 03

R E Oliver
Ruth Oliver

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Sir:

We, Laura S. Lehman, David Tierney, Anastassios D. Retzios, Michael Petrone, David Young, Carol B. Trapnell and Ruth Oliver declare that:

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3. Questcor Pharmaceuticals, Inc. ("Questcor"), GloboMax LLC ("Globomax") and Shire, U.S., Inc. are Assignees of the above-identified application. Questcor is a corporate entity formed by the merger of RiboGene Inc. ("RiboGene") and Cypros Pharmaceutical Corp. in November 1999. Roberts Pharmaceuticals Corporation ("Roberts") merged with Shire Pharmaceuticals Group PLC ("Shire") in December 1999.

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8. As explained in detail hereinbelow, Exhibits A-R, attached hereto, demonstrate that the subject matter claimed in the above-identified patent application was conceived of prior to April 1999, and diligence was exercised from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

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30. We have reviewed Exhibits A-R. We hereby confirm that the work evidenced by the documents of Exhibits A-R and all the acts relied upon in this Declaration to establish a conception of the invention claimed in the above-identified patent application prior to April 1999, and continuing diligence from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

31. We, the co-inventors of the invention claimed in the above-identified patent application further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Respectfully submitted,

Date: _____

_____
Laura S. Lehman

Respectfully submitted,

Date: _____

_____
David Tierney

Respectfully submitted,

Date: _____

_____
Anastassios D. Retzios

Respectfully submitted,

Date: _____

_____
Michael Petrone

Respectfully submitted,

Date: _____

_____
David Young

Respectfully submitted,

Date: 14 May 03

Carol B. Trapnell
Carol B. Trapnell

Respectfully submitted,

Date: _____

_____
Ruth Oliver

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Lehman *et al.*

Serial No.: 09/821,139

Filed: March 29, 2001

For: NASAL ADMINISTRATION OF AGENTS FOR THE TREATMENT OF GASTROPARESIS

Confirmation No.: 5628

Group Art Unit: 1616

Examiner: Haghighatian, M.

Attorney Docket No.: 7960-131

DECLARATION UNDER 37 C.F.R. § 1.131 OF LAURA S. LEHMAN, DAVID TIERNEY, ANASTASSIOS D. RETZIOS, MICHAEL PETRONE, DAVID YOUNG, CAROL B. TRAPNELL AND RUTH OLIVER

Sir:

We, Laura S. Lehman, David Tierney, Anastassios D. Retzios, Michael Petrone, David Young, Carol B. Trapnell and Ruth Oliver declare that:

1. We, together are co-inventors of the invention claimed in the above-identified patent application.

2. We have reviewed the specification and pending claims of the above-identified patent application.

3. Questcor Pharmaceuticals, Inc. ("Questcor"), GloboMax LLC ("Globomax") and Shire, U.S., Inc. are Assignees of the above-identified application. Questcor is a corporate entity formed by the merger of RiboGene Inc. ("RiboGene") and Cypros Pharmaceutical Corp. in November 1999. Roberts Pharmaceuticals Corporation ("Roberts") merged with Shire Pharmaceuticals Group PLC ("Shire") in December 1999.

4. The compound metoclopramide, whose application to gastroparesis is claimed in the above-identified application, was being developed under the tradename, Emitasol® by the cooperative efforts of Roberts (now Shire), RiboGene (now Questcor) and GloboMax.

5. The above-identified patent application claims priority to U.S. provisional application, Serial No. 60/193,181 ("the '181 application"), filed on March 30, 2000.

6. The claims pending in the above-identified patent application recite methods for treating or reducing a symptom of gastroparesis via intranasal administration of metoclopramide. In particular independent Claim 21 recites a method that comprises intranasal administration of a therapeutically effective amount at a daily dosage for about 2 weeks to about 8 weeks, and independent Claim 30 recites a method that comprises administering a therapeutically effective amount at a daily dosage of between about 40 mg/day and about 160 mg/day.

7. To the best of our knowledge and belief, the package insert for Pramidin 10 and Pramidin 20 that is of record in the above-identified patent application, as IDS reference AE, was made available to the public when the product Pramidin was first sold by Crinos Industria Pharmacobiologica S.p.a., in Italy, in April 1999.

8. As explained in detail hereinbelow, Exhibits A-R, attached hereto, demonstrate that the subject matter claimed in the above-identified patent application was conceived of prior to April 1999, and diligence was exercised from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

9. In accordance with standard practice, the dates listed in the documents provided in Exhibits A-R have been redacted.

10. Exhibit A demonstrates that the subject matter of the pending claims was conceived prior to April 1999. Exhibit A is a copy of an excerpt of an Investigational New Drug Application, Form FDA 1571 and Study Synopsis included therein, accompanied by a cover letter from Dr. Haenick, Senior Manager of Regulatory Affairs at Roberts to Dr. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, FDA. Dr. Haenick was an employee of Roberts, acting under the direction of Roberts. We, the co-inventors devised the protocol in Study Synopsis.

11. Exhibits B-R demonstrate that diligence was practiced from prior to April 1999 to subsequent actual reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the parent '181 application. In addition to the dates, confidential, proprietary information has also been redacted for the documents at Exhibits B-R.

12. As discussed hereinbelow, Exhibits B-R, discussed in detail, below, demonstrate diligence in planning a clinical trial protocol that would ultimately demonstrate efficacy and safety of intranasal metoclopramide for the proposed indications at the dosage range for the duration of treatment set forth in the Study Synopsis.

13. Exhibit B is a copy of a letter from Dr. Haenick, Senior Manager of Regulatory Affairs at Roberts to Dr. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, FDA. The letter submits minutes from the End of Phase II meeting with the FDA. An item discussed at the meeting was FDA acceptance of the proposed randomized, double-blind, double-dummy, positive controlled clinical study, as set forth in the Study Synopsis, to compare metoclopramide 10 mg orally before meals and at bedtime and metoclopramide nasal spray at a dose that gives comparable systemic metoclopramide in patients with diabetic gastroparesis.

14. Exhibit C is a copy of meeting minutes from a Roberts/RiboGene Experts Meeting. Items discussed at the meeting include preservation of the blind, the duration of the trial, possible modifications to the symptom assessment tool, and inclusion and exclusion criteria.

15. Exhibit D is a copy of a letter from Dr. Haenick to Dr. Talarico at the FDA. The letter submits revisions to the Phase III protocol. The revised protocol adds a second metoclopramide intranasal dosing group (10 mg four times daily) and a placebo nasal spray group to the study. The proposed study design would consist of two 4-week treatment phases.

16. Exhibit E is a copy of a letter from Dr. Retzios to Dr. Tierney. The letter discusses a desire to get Emitasol® approved in as short a time as possible with proposed dates for a Steering Committee Meeting.

17. Exhibit F is a copy of a letter from Dr. Retzios to Dr. Petrone. The letter refers to published studies of the use of domperidone in the treatment of diabetic gastroparesis, one of which compares the results with non-nasally administered metoclopramide. The letter postulates the possible use of the studies' clinical trial protocol for the testing of intranasal metoclopramide. Clinical trial protocol issues such as randomization, statistical assumptions and questionnaire wording are discussed.

18. Exhibit G is a copy of a letter from Dr. Haenick to Dr. Retzios forwarding budget proposals from two contract research organizations to conduct a Phase III trial.

19. Exhibit H is a copy of a fax from Dr. Haenick to Dr. Retzios forwarding draft meeting minutes from a meeting of the Roberts' Task Force meeting. Meeting discussion topics included Chemistry, Manufacturing and Controls (CMC), nonclinical, and clinical programs. Timelines for development were also established.

20. Exhibit I is a copy of a letter from Dr. Talarico at FDA to Dr. Haenick with protocol recommendations for the proposed clinical trial. The FDA made protocol recommendations including a placebo arm in phase one of the study. Other recommendations included, *inter alia*, the addition of a global assessment of therapy and elimination of the proposed scratch off laminate label.

21. Exhibit J is a copy of minutes of a meeting that took place at Roberts Laboratories, Inc. Representatives from Roberts, RiboGene and GloboMax were present. Items discussed at the meeting included: formulation development, toxicology studies in rabbits and monkeys (a summary provided herein at Exhibits O and P), and review of FDA comments in response to the proposed Phase III clinical trial. The study design was adapted to address FDA recommendations, including the addition of a placebo arm and dropping the withdrawal phase of the study. The proposed, adapted clinical trial was a placebo-controlled, parallel design comparing both the 10 mg and 20 mg metoclopramide nasal spray patients to the placebo group. The duration of therapy was proposed to be 6 weeks. Exhibits O and P, discussed below at paragraphs 26 and 27, demonstrate that the milestones set during this meeting were successfully and timely achieved.

22. Exhibit K is a copy of the GloboMax Response to Dr. Retzios's Comments for Phase III Protocol. The summary provides GloboMax's responses to Dr. Retzio's comments and provides recommendations for the Phase III clinical trial. The recommendations addressed both the secondary and primary objectives of the proposed clinical trial.

23. Exhibit L is a copy of an e-mail from Dr. Retzios to Dr. Petrone (cc: to Dr. Haenick) in which Dr. Retzios discusses updating the definition of "serious" and "unexpected" drug experiences for the proposed Phase III clinical trial.

24. Exhibit M is a copy of an e-mail from Dr. Haenick to Dr. Retzios (cc: to Dr. Petrone and other employees at Roberts) disclosing decisions made regarding the Phase III protocol in light of GloboMax and Dr. Retzios's comments.

25. Exhibit N is a copy of an e-mail from Dr. Retzios to Dr. Petrone (cc: to F. Sasinowski and C. Casamento) disclosing Dr. Retzios's comments on GloboMax's analysis.

26. Exhibit O is a copy of a summary of a Final Report from Covance Laboratories Inc., ("Covance") for a study entitled "3-Month Intranasal Study with Metoclopramide Nasal Spray in Rabbits with a 1-Month Recovery". Covance is a development services company that performs animal testing. The timeline of the study was in accordance with the timeline established at the Robert's Task Force meeting (as discussed in the meeting minutes provided at Exhibit H).

27. Exhibit P is a copy of a summary of a Final Report from Covance, for a study entitled "3-Month Intranasal Study with Metoclopramide Nasal Spray in Cynomolgus Monkeys with a 1-Month Recovery". The timeline of the study was in accordance with the timeline established at the Robert's Task Force meeting (as discussed in the meeting minutes provided at Exhibit H).

28. Exhibit Q is a copy of the agenda for Meeting of the Emitasol® Project Review Meeting. Items on the agenda included, for example, pharmaceutical development, non-clinical toxicology studies, quality control and IND and NDA submissions.

29. Exhibit R is a copy of a summary of the Final Report from Huntingdon Life Sciences. Huntingdon conducted a toxicity study on behalf of Roberts. The study, entitled "Metoclopramide Toxicity Study by Intranasal Administration to Cynomolgus Monkeys for 13 Weeks" was necessary for the FDA.

30. We have reviewed Exhibits A-R. We hereby confirm that the work evidenced by the documents of Exhibits A-R and all the acts relied upon in this Declaration to establish a conception of the invention claimed in the above-identified patent application prior to April 1999, and continuing diligence from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

31. We, the co-inventors of the invention claimed in the above-identified patent application further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Respectfully submitted,

Date: _____

_____
Laura S. Lehman

Respectfully submitted,

Date: _____

_____
David Tierney

Respectfully submitted,

Date: _____

_____
Anastassios D. Retzios

Respectfully submitted,

Date: _____

_____
Michael Petrone

Respectfully submitted,

Date: May 14, 2003

David Young

Respectfully submitted,

Date: _____

Carol B. Trapnell

Respectfully submitted,

Date: _____

Ruth Oliver

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Lehman *et al.*

Serial No.: 09/821,139

Filed: March 29, 2001

For: NASAL ADMINISTRATION OF AGENTS FOR THE TREATMENT OF GASTROPARESIS

Confirmation No.: 5628

Group Art Unit: 1616

Examiner: Haghighatian, M.

Attorney Docket No.: 7960-131

DECLARATION UNDER 37 C.F.R. § 1.131 OF LAURA S. LEHMAN, DAVID TIERNEY, ANASTASSIOS D. RETZIOS, MICHAEL PETRONE, DAVID YOUNG, CAROL B. TRAPNELL AND RUTH OLIVER

Sir:

We, Laura S. Lehman, David Tierney, Anastassios D. Retzios, Michael Petrone, David Young, Carol B. Trapnell and Ruth Oliver declare that:

1. We, together are co-inventors of the invention claimed in the above-identified patent application.

2. We have reviewed the specification and pending claims of the above-identified patent application.

3. Questcor Pharmaceuticals, Inc. ("Questcor"), GloboMax LLC ("Globomax") and Shire, U.S., Inc. are Assignees of the above-identified application. Questcor is a corporate entity formed by the merger of RiboGene Inc. ("RiboGene") and Cypros Pharmaceutical Corp. in November 1999. Roberts Pharmaceuticals Corporation ("Roberts") merged with Shire Pharmaceuticals Group PLC ("Shire") in December 1999.

4. The compound metoclopramide, whose application to gastroparesis is claimed in the above-identified application, was being developed under the tradename, Emitasol® by the cooperative efforts of Roberts (now Shire), RiboGene (now Questcor) and GloboMax.

5. The above-identified patent application claims priority to U.S. provisional application, Serial No. 60/193,181 ("the '181 application"), filed on March 30, 2000.

6. The claims pending in the above-identified patent application recite methods for treating or reducing a symptom of gastroparesis via intranasal administration of metoclopramide. In particular independent Claim 21 recites a method that comprises intranasal administration of a therapeutically effective amount at a daily dosage for about 2 weeks to about 8 weeks, and independent Claim 30 recites a method that comprises administering a therapeutically effective amount at a daily dosage of between about 40 mg/day and about 160 mg/day.

7. To the best of our knowledge and belief, the package insert for Pramidin 10 and Pramidin 20 that is of record in the above-identified patent application, as IDS reference AE, was made available to the public when the product Pramidin was first sold by Crinos Industria Pharmacobiologica S.p.a., in Italy, in April 1999.

8. As explained in detail hereinbelow, Exhibits A-R, attached hereto, demonstrate that the subject matter claimed in the above-identified patent application was conceived of prior to April 1999, and diligence was exercised from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

9. In accordance with standard practice, the dates listed in the documents provided in Exhibits A-R have been redacted.

10. Exhibit A demonstrates that the subject matter of the pending claims was conceived prior to April 1999. Exhibit A is a copy of an excerpt of an Investigational New Drug Application, Form FDA 1571 and Study Synopsis included therein, accompanied by a cover letter from Dr. Haenick, Senior Manager of Regulatory Affairs at Roberts to Dr. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, FDA. Dr. Haenick was an employee of Roberts, acting under the direction of Roberts. We, the co-inventors devised the protocol in Study Synopsis.

11. Exhibits B-R demonstrate that diligence was practiced from prior to April 1999 to subsequent actual reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the parent '181 application. In addition to the dates, confidential, proprietary information has also been redacted for the documents at Exhibits B-R.

12. As discussed hereinbelow, Exhibits B-R, discussed in detail, below, demonstrate diligence in planning a clinical trial protocol that would ultimately demonstrate efficacy and safety of intranasal metoclopramide for the proposed indications at the dosage range for the duration of treatment set forth in the Study Synopsis.

13. Exhibit B is a copy of a letter from Dr. Haenick, Senior Manager of Regulatory Affairs at Roberts to Dr. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, FDA. The letter submits minutes from the End of Phase II meeting with the FDA. An item discussed at the meeting was FDA acceptance of the proposed randomized, double-blind, double-dummy, positive controlled clinical study, as set forth in the Study Synopsis, to compare metoclopramide 10 mg orally before meals and at bedtime and metoclopramide nasal spray at a dose that gives comparable systemic metoclopramide in patients with diabetic gastroparesis.

14. Exhibit C is a copy of meeting minutes from a Roberts/RiboGene Experts Meeting. Items discussed at the meeting include preservation of the blind, the duration of the trial, possible modifications to the symptom assessment tool, and inclusion and exclusion criteria.

15. Exhibit D is a copy of a letter from Dr. Haenick to Dr. Talarico at the FDA. The letter submits revisions to the Phase III protocol. The revised protocol adds a second metoclopramide intranasal dosing group (10 mg four times daily) and a placebo nasal spray group to the study. The proposed study design would consist of two 4-week treatment phases.

16. Exhibit E is a copy of a letter from Dr. Retzios to Dr. Tierney. The letter discusses a desire to get Emitasol® approved in as short a time as possible with proposed dates for a Steering Committee Meeting.

17. Exhibit F is a copy of a letter from Dr. Retzios to Dr. Petrone. The letter refers to published studies of the use of domperidone in the treatment of diabetic gastroparesis, one of which compares the results with non-nasally administered metoclopramide. The letter postulates the possible use of the studies' clinical trial protocol for the testing of intranasal metoclopramide. Clinical trial protocol issues such as randomization, statistical assumptions and questionnaire wording are discussed.

18. Exhibit G is a copy of a letter from Dr. Haenick to Dr. Retzios forwarding budget proposals from two contract research organizations to conduct a Phase III trial.

19. Exhibit H is a copy of a fax from Dr. Haenick to Dr. Retzios forwarding draft meeting minutes from a meeting of the Roberts' Task Force meeting. Meeting discussion topics included Chemistry, Manufacturing and Controls (CMC), nonclinical, and clinical programs. Timelines for development were also established.

20. Exhibit I is a copy of a letter from Dr. Talarico at FDA to Dr. Haenick with protocol recommendations for the proposed clinical trial. The FDA made protocol recommendations including a placebo arm in phase one of the study. Other recommendations included, *inter alia*, the addition of a global assessment of therapy and elimination of the proposed scratch off laminate label.

21. Exhibit J is a copy of minutes of a meeting that took place at Roberts Laboratories, Inc. Representatives from Roberts, RiboGene and GloboMax were present. Items discussed at the meeting included: formulation development, toxicology studies in rabbits and monkeys (a summary provided herein at Exhibits O and P), and review of FDA comments in response to the proposed Phase III clinical trial. The study design was adapted to address FDA recommendations, including the addition of a placebo arm and dropping the withdrawal phase of the study. The proposed, adapted clinical trial was a placebo-controlled, parallel design comparing both the 10 mg and 20 mg metoclopramide nasal spray patients to the placebo group. The duration of therapy was proposed to be 6 weeks. Exhibits O and P, discussed below at paragraphs 26 and 27, demonstrate that the milestones set during this meeting were successfully and timely achieved.

22. Exhibit K is a copy of the GloboMax Response to Dr. Retzios's Comments for Phase III Protocol. The summary provides GloboMax's responses to Dr. Retzio's comments and provides recommendations for the Phase III clinical trial. The recommendations addressed both the secondary and primary objectives of the proposed clinical trial.

23. Exhibit L is a copy of an e-mail from Dr. Retzios to Dr. Petrone (cc: to Dr. Haenick) in which Dr. Retzios discusses updating the definition of "serious" and "unexpected" drug experiences for the proposed Phase III clinical trial.

24. Exhibit M is a copy of an e-mail from Dr. Haenick to Dr. Retzios (cc: to Dr. Petrone and other employees at Roberts) disclosing decisions made regarding the Phase III protocol in light of GloboMax and Dr. Retzios's comments.

25. Exhibit N is a copy of an e-mail from Dr. Retzios to Dr. Petrone (cc: to F. Sasinowski and C. Casamento) disclosing Dr. Retzios's comments on GloboMax's analysis.

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27. Exhibit P is a copy of a summary of a Final Report from Covance, for a study entitled "3-Month Intranasal Study with Metoclopramide Nasal Spray in Cynomolgus Monkeys with a 1-Month Recovery". The timeline of the study was in accordance with the timeline established at the Robert's Task Force meeting (as discussed in the meeting minutes provided at Exhibit H).

28. Exhibit Q is a copy of the agenda for Meeting of the Emitasol® Project Review Meeting. Items on the agenda included, for example, pharmaceutical development, non-clinical toxicology studies, quality control and IND and NDA submissions.

29. Exhibit R is a copy of a summary of the Final Report from Huntingdon Life Sciences. Huntingdon conducted a toxicity study on behalf of Roberts. The study, entitled "Metoclopramide Toxicity Study by Intranasal Administration to Cynomolgus Monkeys for 13 Weeks" was necessary for the FDA.

30. We have reviewed Exhibits A-R. We hereby confirm that the work evidenced by the documents of Exhibits A-R and all the acts relied upon in this Declaration to establish a conception of the invention claimed in the above-identified patent application prior to April 1999, and continuing diligence from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

31. We, the co-inventors of the invention claimed in the above-identified patent application further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Respectfully submitted,

Date: _____

_____
Laura S. Lehman

Respectfully submitted,

Date: _____

_____
David Tierney

Respectfully submitted,

Date: May 12, 2003

_____
Anastassios D. Retzios

Respectfully submitted,

Date: _____

_____
Michael Petrone

Respectfully submitted,

Date: _____

_____
David Young

Respectfully submitted,

Date: _____

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Carol B. Trapnell

Respectfully submitted,

Date: _____

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Ruth Oliver

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Lehman *et al.*

Serial No.: 09/821,139

Filed: March 29, 2001

For: NASAL ADMINISTRATION OF AGENTS FOR THE TREATMENT OF GASTROPARESIS

Confirmation No.: 5628

Group Art Unit: 1616

Examiner: Haghighatian, M.

Attorney Docket No.: 7960-131

DECLARATION UNDER 37 C.F.R. § 1.131 OF LAURA S. LEHMAN, DAVID TIERNEY, ANASTASSIOS D. RETZIOS, MICHAEL PETRONE, DAVID YOUNG, CAROL B. TRAPNELL AND RUTH OLIVER

Sir:

We, Laura S. Lehman, David Tierney, Anastassios D. Retzios, Michael Petrone, David Young, Carol B. Trapnell and Ruth Oliver declare that:

1. We, together are co-inventors of the invention claimed in the above-identified patent application.

2. We have reviewed the specification and pending claims of the above-identified patent application.

3. Questcor Pharmaceuticals, Inc. ("Questcor"), GloboMax LLC ("Globomax") and Shire, U.S., Inc. are Assignees of the above-identified application. Questcor is a corporate entity formed by the merger of RiboGene Inc. ("RiboGene") and Cypros Pharmaceutical Corp. in November 1999. Roberts Pharmaceuticals Corporation ("Roberts") merged with Shire Pharmaceuticals Group PLC ("Shire") in December 1999.

4. The compound metoclopramide, whose application to gastroparesis is claimed in the above-identified application, was being developed under the tradename, Emitasol® by the cooperative efforts of Roberts (now Shire), RiboGene (now Questcor) and GloboMax.

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8. As explained in detail hereinbelow, Exhibits A-R, attached hereto, demonstrate that the subject matter claimed in the above-identified patent application was conceived of prior to April 1999, and diligence was exercised from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

9. In accordance with standard practice, the dates listed in the documents provided in Exhibits A-R have been redacted.

10. Exhibit A demonstrates that the subject matter of the pending claims was conceived prior to April 1999. Exhibit A is a copy of an excerpt of an Investigational New Drug Application, Form FDA 1571 and Study Synopsis included therein, accompanied by a cover letter from Dr. Haenick, Senior Manager of Regulatory Affairs at Roberts to Dr. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, FDA. Dr. Haenick was an employee of Roberts, acting under the direction of Roberts. We, the co-inventors devised the protocol in Study Synopsis.

11. Exhibits B-R demonstrate that diligence was practiced from prior to April 1999 to subsequent actual reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the parent '181 application. In addition to the dates, confidential, proprietary information has also been redacted for the documents at Exhibits B-R.

12. As discussed hereinbelow, Exhibits B-R, discussed in detail, below, demonstrate diligence in planning a clinical trial protocol that would ultimately demonstrate efficacy and safety of intranasal metoclopramide for the proposed indications at the dosage range for the duration of treatment set forth in the Study Synopsis.

13. Exhibit B is a copy of a letter from Dr. Haenick, Senior Manager of Regulatory Affairs at Roberts to Dr. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, FDA. The letter submits minutes from the End of Phase II meeting with the FDA. An item discussed at the meeting was FDA acceptance of the proposed randomized, double-blind, double-dummy, positive controlled clinical study, as set forth in the Study Synopsis, to compare metoclopramide 10 mg orally before meals and at bedtime and metoclopramide nasal spray at a dose that gives comparable systemic metoclopramide in patients with diabetic gastroparesis.

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23. Exhibit L is a copy of an e-mail from Dr. Retzios to Dr. Petrone (cc: to Dr. Haenick) in which Dr. Retzios discusses updating the definition of "serious" and "unexpected" drug experiences for the proposed Phase III clinical trial.

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28. Exhibit Q is a copy of the agenda for Meeting of the Emitasol® Project Review Meeting. Items on the agenda included, for example, pharmaceutical development, non-clinical toxicology studies, quality control and IND and NDA submissions.

29. Exhibit R is a copy of a summary of the Final Report from Huntingdon Life Sciences. Huntingdon conducted a toxicity study on behalf of Roberts. The study, entitled "Metoclopramide Toxicity Study by Intranasal Administration to Cynomolgus Monkeys for 13 Weeks" was necessary for the FDA.

30. We have reviewed Exhibits A-R. We hereby confirm that the work evidenced by the documents of Exhibits A-R and all the acts relied upon in this Declaration to establish a conception of the invention claimed in the above-identified patent application prior to April 1999, and continuing diligence from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

31. We, the co-inventors of the invention claimed in the above-identified patent application further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Respectfully submitted,

Date: _____

_____
Laura S. Lehman

Respectfully submitted,

Date: _____

_____
David Tierney

Respectfully submitted,

Date: _____

_____
Anastassios D. Retzios

Respectfully submitted,

Date: 5/24/03

Michael Petrone
Michael Petrone

Respectfully submitted,

Date: _____

_____
David Young

Respectfully submitted,

Date: _____

_____
Carol B. Trapnell

Respectfully submitted,

Date: _____

_____
Ruth Oliver

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Lehman *et al.*

Serial No.: 09/821,139

Filed: March 29, 2001

For: NASAL ADMINISTRATION OF AGENTS FOR THE TREATMENT OF GASTROPARESIS

Confirmation No.: 5628

Group Art Unit: 1616

Examiner: Haghighatian, M.

Attorney Docket No.: 7960-131

DECLARATION UNDER 37 C.F.R. § 1.131 OF LAURA S. LEHMAN, DAVID TIERNEY, ANASTASSIOS D. RETZIOS, MICHAEL PETRONE, DAVID YOUNG, CAROL B. TRAPNELL AND RUTH OLIVER

Sir:

We, Laura S. Lehman, David Tierney, Anastassios D. Retzios, Michael Petrone, David Young, Carol B. Trapnell and Ruth Oliver declare that:

1. We, together are co-inventors of the invention claimed in the above-identified patent application.

2. We have reviewed the specification and pending claims of the above-identified patent application.

3. Questcor Pharmaceuticals, Inc. ("Questcor"), GloboMax LLC ("Globomax") and Shire, U.S., Inc. are Assignees of the above-identified application. Questcor is a corporate entity formed by the merger of RiboGene Inc. ("RiboGene") and Cypros Pharmaceutical Corp. in November 1999. Roberts Pharmaceuticals Corporation ("Roberts") merged with Shire Pharmaceuticals Group PLC ("Shire") in December 1999.

4. The compound metoclopramide, whose application to gastroparesis is claimed in the above-identified application, was being developed under the tradename, Emitasol® by the cooperative efforts of Roberts (now Shire), RiboGene (now Questcor) and GloboMax.

5. The above-identified patent application claims priority to U.S. provisional application, Serial No. 60/193,181 ("the '181 application"), filed on March 30, 2000.

6. The claims pending in the above-identified patent application recite methods for treating or reducing a symptom of gastroparesis via intranasal administration of metoclopramide. In particular independent Claim 21 recites a method that comprises intranasal administration of a therapeutically effective amount at a daily dosage for about 2 weeks to about 8 weeks, and independent Claim 30 recites a method that comprises administering a therapeutically effective amount at a daily dosage of between about 40 mg/day and about 160 mg/day.

7. To the best of our knowledge and belief, the package insert for Pramidin 10 and Pramidin 20 that is of record in the above-identified patent application, as IDS reference AE, was made available to the public when the product Pramidin was first sold by Crinos Industria Pharmacobiologica S.p.a., in Italy, in April 1999.

8. As explained in detail hereinbelow, Exhibits A-R, attached hereto, demonstrate that the subject matter claimed in the above-identified patent application was conceived of prior to April 1999, and diligence was exercised from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

9. In accordance with standard practice, the dates listed in the documents provided in Exhibits A-R have been redacted.

10. Exhibit A demonstrates that the subject matter of the pending claims was conceived prior to April 1999. Exhibit A is a copy of an excerpt of an Investigational New Drug Application, Form FDA 1571 and Study Synopsis included therein, accompanied by a cover letter from Dr. Haenick, Senior Manager of Regulatory Affairs at Roberts to Dr. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, FDA. Dr. Haenick was an employee of Roberts, acting under the direction of Roberts. We, the co-inventors devised the protocol in Study Synopsis.

11. Exhibits B-R demonstrate that diligence was practiced from prior to April 1999 to subsequent actual reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the parent '181 application. In addition to the dates, confidential, proprietary information has also been redacted for the documents at Exhibits B-R.

12. As discussed hereinbelow, Exhibits B-R, discussed in detail, below, demonstrate diligence in planning a clinical trial protocol that would ultimately demonstrate efficacy and safety of intranasal metoclopramide for the proposed indications at the dosage range for the duration of treatment set forth in the Study Synopsis.

13. Exhibit B is a copy of a letter from Dr. Haenick, Senior Manager of Regulatory Affairs at Roberts to Dr. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, FDA. The letter submits minutes from the End of Phase II meeting with the FDA. An item discussed at the meeting was FDA acceptance of the proposed randomized, double-blind, double-dummy, positive controlled clinical study, as set forth in the Study Synopsis, to compare metoclopramide 10 mg orally before meals and at bedtime and metoclopramide nasal spray at a dose that gives comparable systemic metoclopramide in patients with diabetic gastroparesis.

14. Exhibit C is a copy of meeting minutes from a Roberts/RiboGene Experts Meeting. Items discussed at the meeting include preservation of the blind, the duration of the trial, possible modifications to the symptom assessment tool, and inclusion and exclusion criteria.

15. Exhibit D is a copy of a letter from Dr. Haenick to Dr. Talarico at the FDA. The letter submits revisions to the Phase III protocol. The revised protocol adds a second metoclopramide intranasal dosing group (10 mg four times daily) and a placebo nasal spray group to the study. The proposed study design would consist of two 4-week treatment phases.

16. Exhibit E is a copy of a letter from Dr. Retzios to Dr. Tierney. The letter discusses a desire to get Emitasol® approved in as short a time as possible with proposed dates for a Steering Committee Meeting.

17. Exhibit F is a copy of a letter from Dr. Retzios to Dr. Petrone. The letter refers to published studies of the use of domperidone in the treatment of diabetic gastroparesis, one of which compares the results with non-nasally administered metoclopramide. The letter postulates the possible use of the studies' clinical trial protocol for the testing of intranasal metoclopramide. Clinical trial protocol issues such as randomization, statistical assumptions and questionnaire wording are discussed.

18. Exhibit G is a copy of a letter from Dr. Haenick to Dr. Retzios forwarding budget proposals from two contract research organizations to conduct a Phase III trial.

19. Exhibit H is a copy of a fax from Dr. Haenick to Dr. Retzios forwarding draft meeting minutes from a meeting of the Roberts' Task Force meeting. Meeting discussion topics included Chemistry, Manufacturing and Controls (CMC), nonclinical, and clinical programs. Timelines for development were also established.

20. Exhibit I is a copy of a letter from Dr. Talarico at FDA to Dr. Haenick with protocol recommendations for the proposed clinical trial. The FDA made protocol recommendations including a placebo arm in phase one of the study. Other recommendations included, *inter alia*, the addition of a global assessment of therapy and elimination of the proposed scratch off laminate label.

21. Exhibit J is a copy of minutes of a meeting that took place at Roberts Laboratories, Inc. Representatives from Roberts, RiboGene and GloboMax were present. Items discussed at the meeting included: formulation development, toxicology studies in rabbits and monkeys (a summary provided herein at Exhibits O and P), and review of FDA comments in response to the proposed Phase III clinical trial. The study design was adapted to address FDA recommendations, including the addition of a placebo arm and dropping the withdrawal phase of the study. The proposed, adapted clinical trial was a placebo-controlled, parallel design comparing both the 10 mg and 20 mg metoclopramide nasal spray patients to the placebo group. The duration of therapy was proposed to be 6 weeks. Exhibits O and P, discussed below at paragraphs 26 and 27, demonstrate that the milestones set during this meeting were successfully and timely achieved.

22. Exhibit K is a copy of the GloboMax Response to Dr. Retzios's Comments for Phase III Protocol. The summary provides GloboMax's responses to Dr. Retzio's comments and provides recommendations for the Phase III clinical trial. The recommendations addressed both the secondary and primary objectives of the proposed clinical trial.

23. Exhibit L is a copy of an e-mail from Dr. Retzios to Dr. Petrone (cc: to Dr. Haenick) in which Dr. Retzios discusses updating the definition of "serious" and "unexpected" drug experiences for the proposed Phase III clinical trial.

24. Exhibit M is a copy of an e-mail from Dr. Haenick to Dr. Retzios (cc: to Dr. Petrone and other employees at Roberts) disclosing decisions made regarding the Phase III protocol in light of GloboMax and Dr. Retzios's comments.

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30. We have reviewed Exhibits A-R. We hereby confirm that the work evidenced by the documents of Exhibits A-R and all the acts relied upon in this Declaration to establish a conception of the invention claimed in the above-identified patent application prior to April 1999, and continuing diligence from prior to April 1999 to subsequent reduction to practice of the claimed subject matter and/or until the March 30, 2000 filing date of the '181 application.

31. We, the co-inventors of the invention claimed in the above-identified patent application further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Respectfully submitted,

Date: _____

_____
Laura S. Lehman

Respectfully submitted,

Date: 5/9/2003

_____
David Tierney

Respectfully submitted,

Date: _____

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Anastassios D. Retzios

Respectfully submitted,

Date: _____

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Michael Petrone

Respectfully submitted,

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David Young

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Ruth Oliver